

Fig. S1. Quality control of the human and mouse spatial transcriptomics datasets. a, Dot plot showing the expression of selected marker genes in the cortical layer clusters from the human ST dataset. **b**, Dot plot showing the expression of selected marker genes in the clusters from the mouse ST dataset. **c**, The number of spots profiled in each cluster, and the proportion of diagnosis attributed to each of the clusters. **d-e**, Distributions of the number of UMI captured in each of the mouse (**d**) and human (**e**) ST clusters. **f-g**, Distributions of the number of UMI captured in each of the human (**f**) and mouse (**g**) samples. **h-i**, Distributions of ex-vivo activation ¹ UCell² scores in each of the ST clusters in the human (**h**) and mouse (**i** clusters). For box and whisker plots, box boundaries and line correspond to the interquartile range (IQR) and median, respectively. Whiskers extend to the lowest or highest data points that are no further than 1.5 times the IQR from the box boundaries.

Control, F, 64	Control, F, 74	Control, F, 74	Control, F, 79	Control, F, 90	Control, M, 70	Control, M, 73
Control, M, 79	Control, M, 83	Control, M, 90	earlyAD, F, 87	earlyAD, F, 89	earlyAD, F, 90	earlyAD, M, 79
earlyAD, M, 80	earlyAD, M, 86	earlyAD, M, 87	earlyAD, M, 90	earlyAD, M, 90	AD, F, 87	AD, F, 89
AD, F, 89	AD, F, 90	AD, F, 90	AD, F, 90	AD, M, 80	AD, M, 86	AD, M, 90
AD, F, 89	AD, F, 90	AD, F, 90	AD, F, 90	AD, M, 80	AD, M, 86	AD, M, 90
AD, F, 89			AD, F, 90			
AD, M, 90		AD_DS, F, 55	AD_DS, F, 56			

Fig. S2. Clustering results in the human ST dataset. We used BayesSpace³ to jointly cluster spatial transcriptomic spots in the 39 samples from the human dataset based on their transcriptomic content as well as their spatial information (Methods). This process resulted in nine clusters, which we annotated based on marker gene expression and anatomic location. Each human ST sample is shown here with each spot colored by BayesSpace cluster assignment. We organized the samples in this plot by disease status, sex, and age.

4mo, 5X, F	4mo, 5X, F	4mo, 5X, F	4mo, 5X, F	4mo, 5X, F	4mo, 5X, M	4mo, 5X, M	4mo, 5X, M
4mo, 5X, M	4mo, 5X, M	4mo, WT, F	4mo, WT, F	4mo, WT, F	4mo, WT, F	4mo, WT, F	4mo, WT, M
4mo, WT, M	4mo, WT, M	4mo, WT, M	4mo, WT, M	6mo, 5X, F	6mo, 5X, F	6mo, 5X, F	6mo, 5X, F
6mo, 5X, F	6mo, 5X, M	6mo, 5X, M	6mo, 5X, M	6mo, 5X, M	6mo, 5X, M	6mo, WT, F	6mo, WT, F
6mo, WT, F	6mo, WT, F	6mo, WT, F	6mo, WT, M	6mo, WT, M	6mo, WT, M	6mo, WT, M	6mo, WT, M
				G			
8mo, 5X, F	8mo, 5X, F	8mo, 5X, F	8mo, 5X, F	8mo, 5X, F	8mo, 5X, M	8mo, 5X, M	8mo, 5X, M
				63			
8mo, 5X, M	8mo, 5X, M	8mo, WT, F	8mo, WT, F	8mo, WT, F	8mo, WT, F	8mo, WT, F	8mo, WT, M
C C C C C C C C C C C C C C C C C C C							
8mo, WT, M	8mo, WT, M	8mo, WT, M	8mo, WT, M	12mo, 5X, F	12mo, 5X, F	12mo, 5X, F	12mo, 5X, F
	6.5						
12mo, 5X, F	12mo, 5X, F	12mo, 5X, F	12mo, 5X, M	12mo, 5X, M	12mo, 5X, M	12mo, 5X, M	12mo, 5X, M
12mo, WT, F	12mo, WT, F	12mo, WT, F	12mo, WT, M	12mo, WT, M	12mo, WT, M	12mo, WT, M	12mo, WT, M
	WM1 WM2 WM-cerebral-	low qual	ity la	ateral-ventricle 📕 ctx-	-deep-layers 📃 hipp	olfactory ocampus ocampus–pyramidal	

Fig. S3. Clustering results in the mouse ST dataset. We used BayesSpace³ to jointly cluster spatial transcriptomic spots in the 80 samples from the mouse dataset based on their transcriptomic content as well as their spatial information (Methods). This process resulted in 15 clusters, which we annotated based on marker gene expression and anatomic location. Each mouse ST sample is shown here with each spot colored by BayesSpace cluster assignment. We organized the samples in this plot by disease age, genotype, and sex.

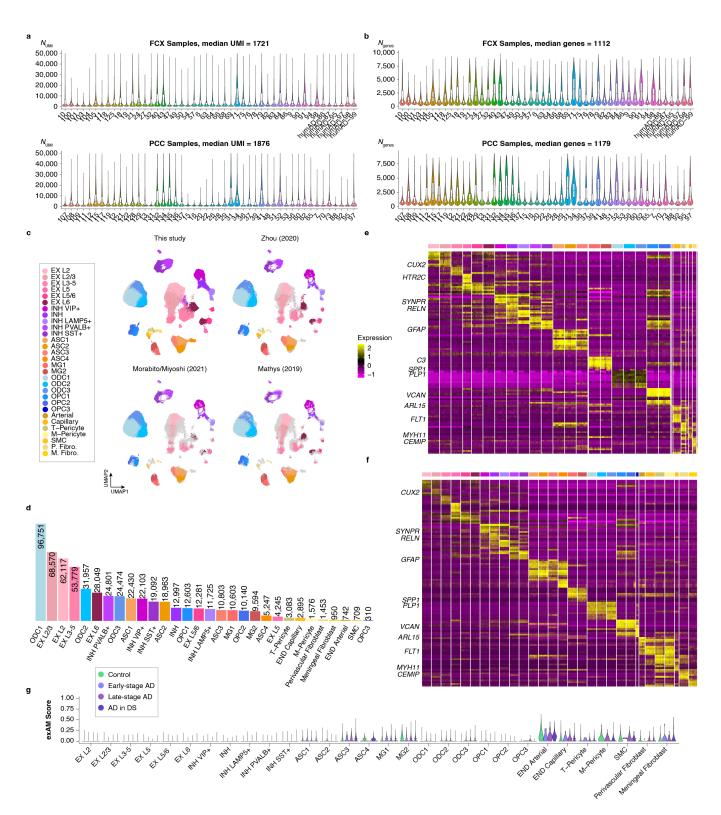


Fig. S4. Quality control of the integrated snRNA-seq dataset. a, Distributions of the number of UMI captured in each snRNA-seq sample for the frontal cortex (FCX, top) and the posterior cingulate cortex (PCC, bottom). **b**, Distributions of the number of genes captured in each snRNA-seq sample for the FCX (top) and the PCC (bottom). **c**, UMAP dimensionality reduction plot of the integrated snRNA-seq dataset comprised of the data generated in this study and three previous snRNA-seq datasets of AD. The UMAP plot is faceted by study of origin, and colored by cluster annotations. **d**, Bar plot showing the number of nuclei in each of the snRNA-seq clusters. **e**, Heatmap showing the expression of the top 5 marker genes ranked by effect size in the snRNA-seq dataset. These marker genes were identified using only the data generated in this study, and this heatmap only shows expression data from these nuclei (Methods). **f**, Heatmap showing the expression of the same genes as in panel (**e**) in the three other snRNA-seq datasets. **g**, Distributions of ex-vivo activation¹ UCell² scores in each of the snRNA-seq clusters. For box and whisker plots, box boundaries and line correspond to the interquartile range (IQR) and median, respectively. Whiskers extend to the lowest or highest data points that are no further than 1.5 times the IQR from the box boundaries.

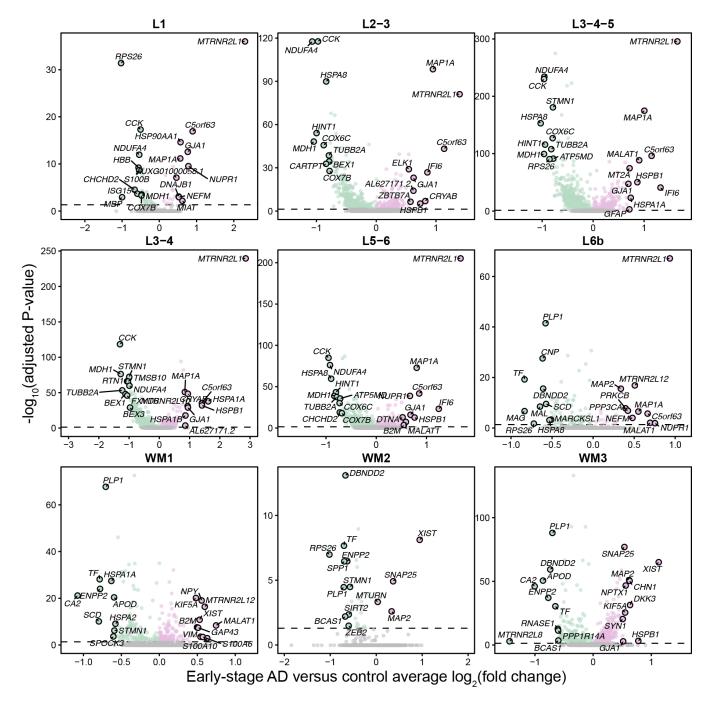


Fig. S5. Early-stage AD versus control DEGs in the ST dataset. Volcano plots show the adjusted significance levels and effect sizes from the differential gene expression comparisons between early-stage AD cases versus cognitively normal controls in the human ST dataset. The results are shown for the differential gene expression analysis in each of the nine spatial clusters. The top and bottom ten genes by effect size are annotated.

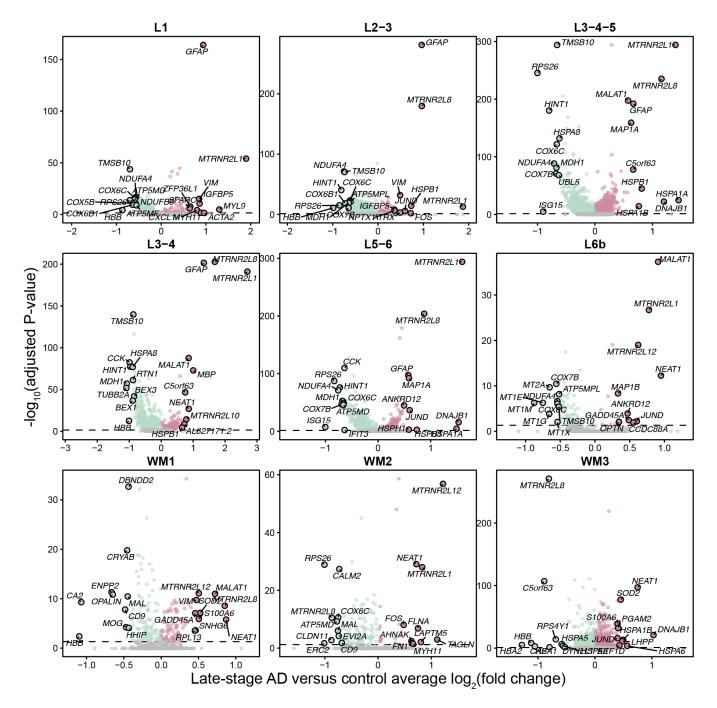


Fig. S6. Late-stage AD versus control DEGs in the ST dataset. Volcano plots show the adjusted significance levels and effect sizes from the differential gene expression comparisons between late-stage AD cases versus cognitively normal controls in the human ST dataset. The results are shown for the differential gene expression analysis in each of the nine spatial clusters. The top and bottom ten genes by effect size are annotated.

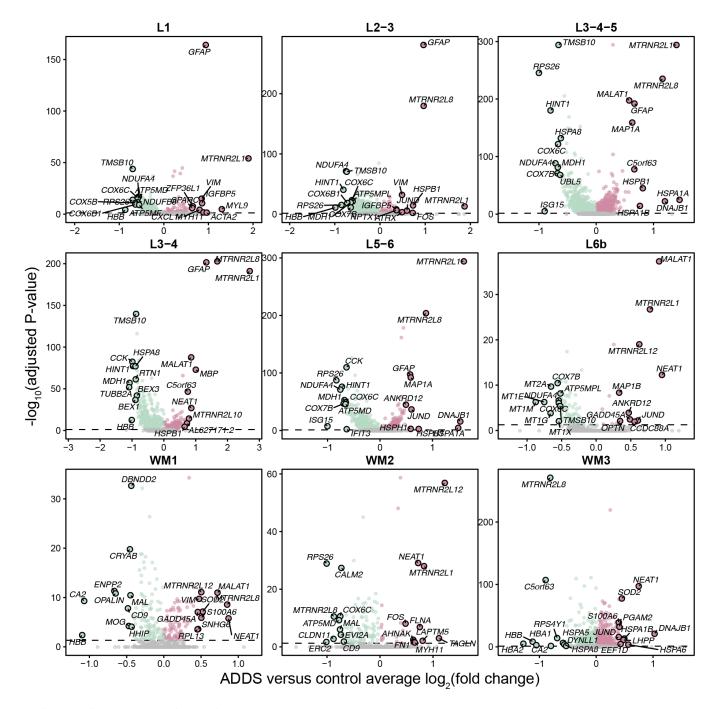


Fig. S7. AD in DS versus control DEGs in the ST dataset. Volcano plots show the adjusted significance levels and effect sizes from the differential gene expression comparisons between AD in DS cases versus cognitively normal controls in the human ST dataset. The results are shown for the differential gene expression analysis in each of the nine spatial clusters. The top and bottom ten genes by effect size are annotated.

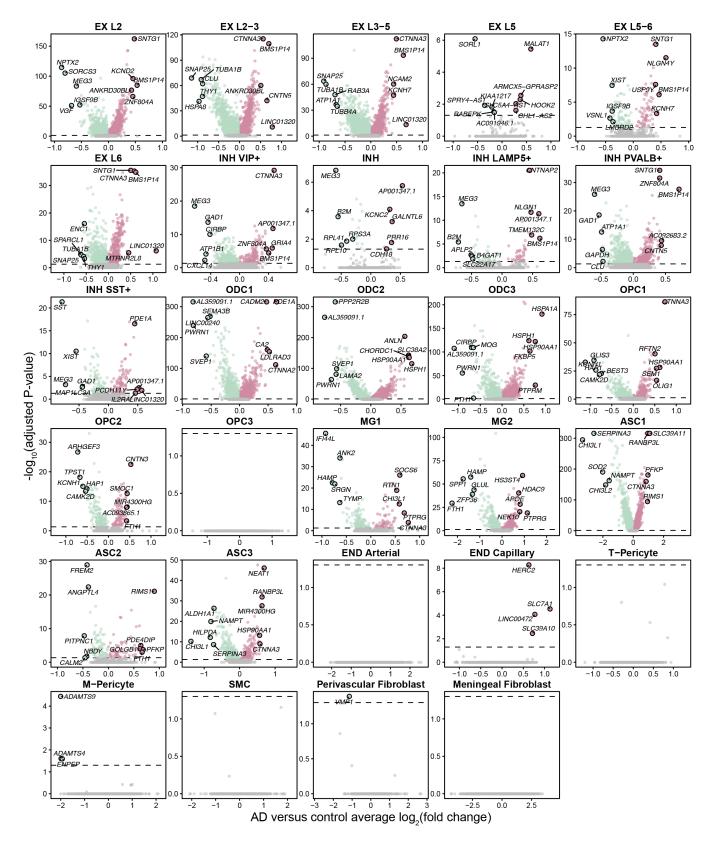


Fig. S8. Late-stage AD versus control DEGs in the snRNA-seq dataset. Volcano plots show the adjusted significance levels and effect sizes from the differential gene expression comparisons between late-stage AD cases versus cognitively normal controls from the integrated analysis of the three previously published snRNA-seq datasets. The results are shown for the differential gene expression analysis in each of the snRNA-seq clusters. The top and bottom five genes by effect size are annotated.

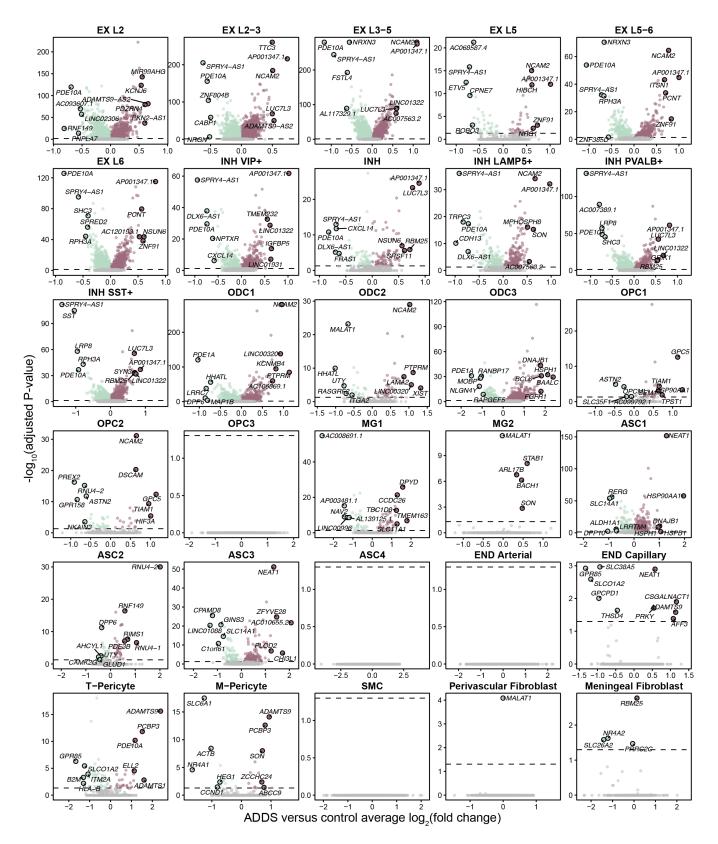


Fig. S9. AD in DS versus control DEGs in the FCX snRNA-seq dataset. Volcano plots show the adjusted significance levels and effect sizes from the differential gene expression comparisons between AD in DS cases versus cognitively normal controls in the frontal cortex (FCX) snRNA-seq dataset. The results are shown for the differential gene expression analysis in each of the snRNA-seq clusters. The top and bottom five genes by effect size are annotated.

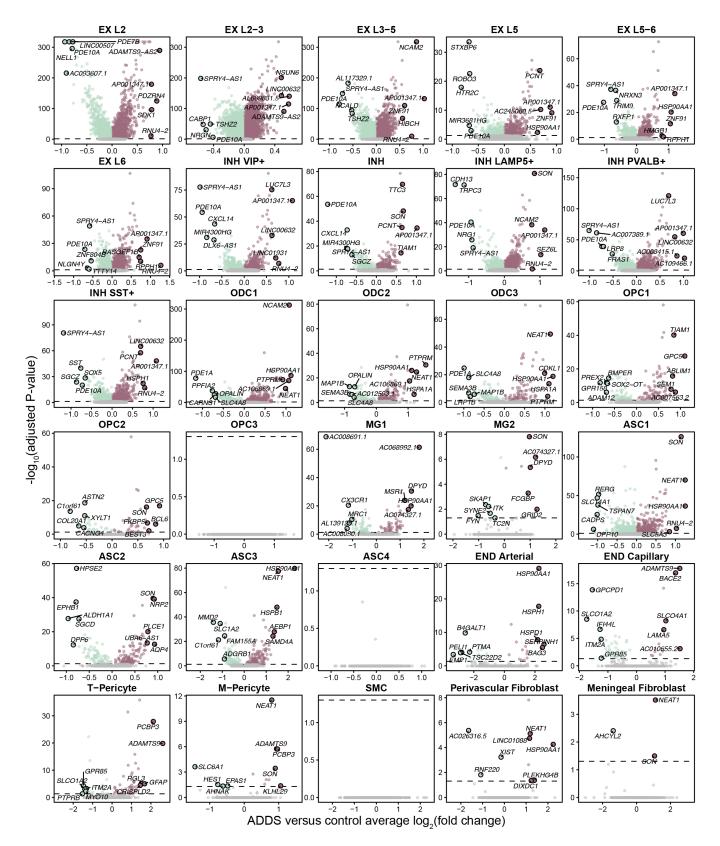


Fig. S10. AD in DS versus control DEGs in the PCC snRNA-seq dataset Volcano plots show the adjusted significance levels and effect sizes from the differential gene expression comparisons between AD in DS cases versus cognitively normal controls in the posterior cingulate cortex (PCC) snRNA-seq dataset. The results are shown for the differential gene expression analysis in each of the snRNA-seq clusters. The top and bottom five genes by effect size are annotated.

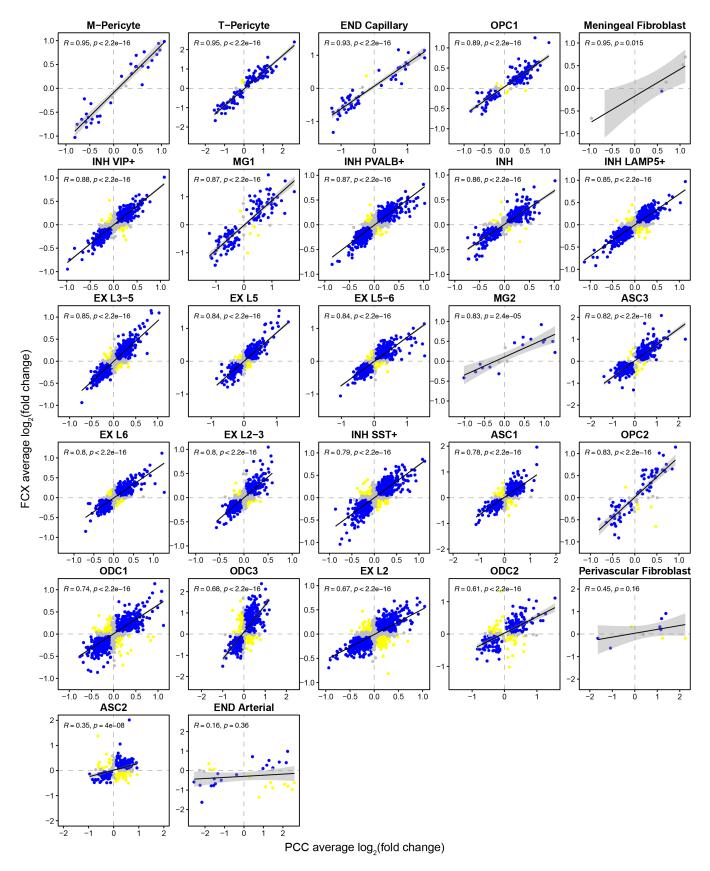


Fig. S11. Comparison of snRNA-seq AD in DS versus control DEG effect sizes in the PCC and FCX Comparison of differential expression effect sizes from AD in DS versus control in the PCC and FCX snRNA-seq data. Genes that were statistically significant (adjusted p-value < 0.05) in either comparison were included in this analysis. Genes are colored blue if the direction is consistent, yellow if inconsistent, and grey if the absolute effect sizes were smaller than 0.05. Black line represents a linear regression with a 95% confidence interval shown in grey. Pearson correlation coefficients are shown in the upper left corner of each panel.

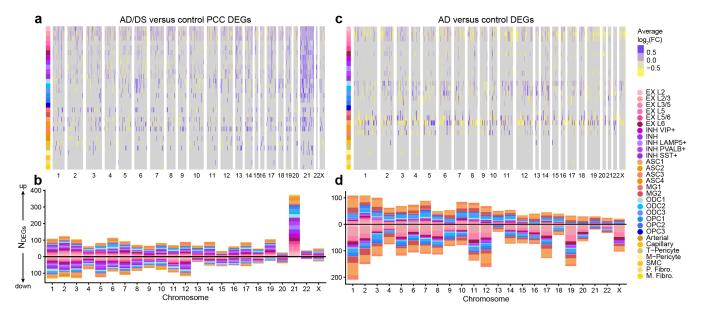


Fig. S12. snRNA-seq DEGs examined by chromosome a, Heatmap colored by effect size from the PCC AD in DS versus control differential gene expression analysis, with genes stratified by chromosome and by spatial region. Statistically significant (FDR < 0.05) genes with an absolute average log2(fold-change) >= 0.25 in at least one region are shown. **b**, Stacked bar chart showing the number of PCC AD in DS versus control DEGs in each snRNA-seq cluster stratified by chromosome. **c**, Heatmap colored by effect size from the late-stage AD versus control differential gene expression analysis, with genes stratified by chromosome and by spatial region. Statistically significant (FDR < 0.05) genes with an absolute average log2(fold-change) >= 0.25 in at least one region are shown. **d**, Stacked bar chart showing the number of late-stage AD versus control DEGs in each snRNA-seq cluster stratified by chromosome and by spatial region. Statistically significant (FDR < 0.05) genes with an absolute average log2(fold-change) >= 0.25 in at least one region are shown. **d**, Stacked bar chart showing the number of late-stage AD versus control DEGs in each snRNA-seq cluster stratified by chromosome.

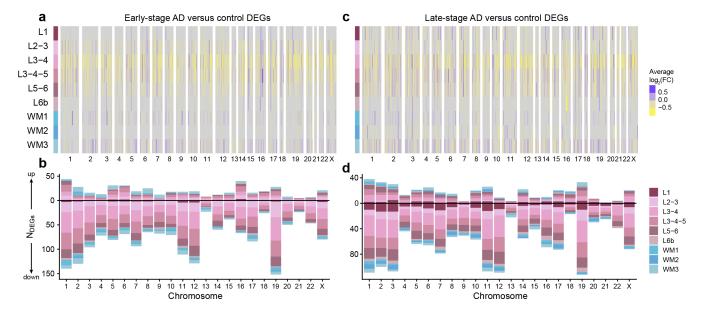


Fig. S13. Gene set overlap analysis of spatial transcriptomics DEGs from different disease groups a, Heatmap colored by effect size from the spatial transcriptomic early-stage AD versus control differential gene expression analysis, with genes stratified by chromosome and by spatial region. Statistically significant (FDR < 0.05) genes with an absolute average log2(fold-change) >= 0.25 in at least one region are shown. **b**, Stacked bar chart showing the number of spatial transcriptomic early-stage AD control DEGs in each spatial cluster stratified by chromosome and by spatial region. Statistically significant (FDR < 0.05) genes with an absolute average log2(fold-change) >= 0.25 in at least one region are shown. **b**, Stacked bar chart showing the number of spatial transcriptomic early-stage AD versus control differential gene expression analysis, with genes stratified by chromosome and by spatial region. Statistically significant (FDR < 0.05) genes with an absolute average log2(fold-change) >= 0.25 in at least one region are shown. **d**, Stacked bar chart showing the number of spatial transcriptomic early-stage AD versus control DEGs in each spatial cluster stratified by chromosome and by spatial region. Statistically significant (FDR < 0.05) genes with an absolute average log2(fold-change) >= 0.25 in at least one region are shown. **d**, Stacked bar chart showing the number of spatial transcriptomic early-stage AD versus control DEGs in each spatial cluster stratified by chromosome.

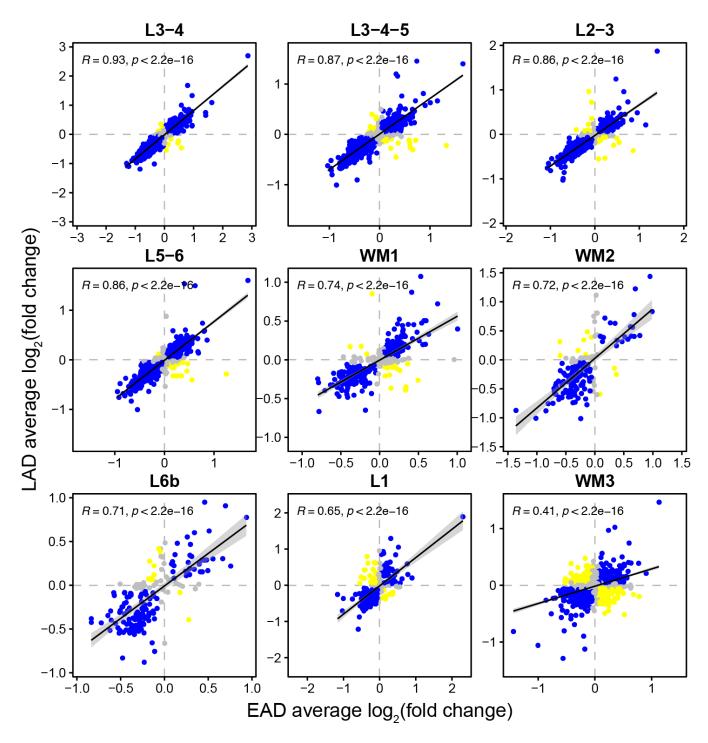


Fig. S14. Comparison of spatial transcriptomic DEG effect sizes between early-stage AD and late-stage AD Comparison of differential expression effect sizes from early-stage AD versus control and late-stage AD versus control. Genes that were statistically significant (adjusted p-value < 0.05) in either comparison were included in this analysis. Genes are colored blue if the direction is consistent, yellow if inconsistent, and grey if the absolute effect sizes were smaller than 0.05. Black line represents a linear regression with a 95% confidence interval shown in grey. Pearson correlation coefficients are shown in the upper left corner of each panel.

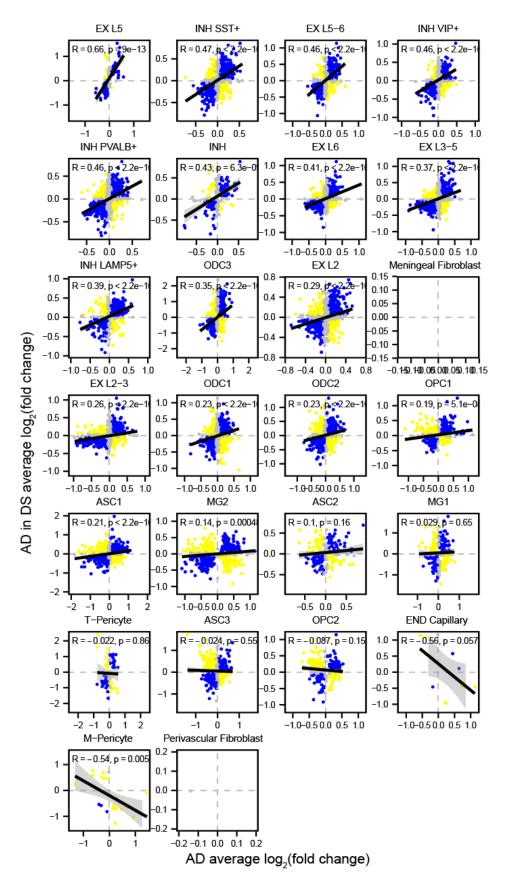


Fig. S15. Comparison of snRNA-seq DEG effect sizes between sporadic AD and AD in DS Comparison of differential expression effect sizes from sAD versus control and AD in DS versus control. Genes that were statistically significant (adjusted p-value < 0.05) in either comparison were included in this analysis. Genes are colored blue if the direction is consistent, yellow if inconsistent, and grey if the absolute effect sizes were smaller than 0.05. Black line represents a linear regression with a 95% confidence interval shown in grey. Pearson correlation coefficients are shown in the upper left corner of each panel.

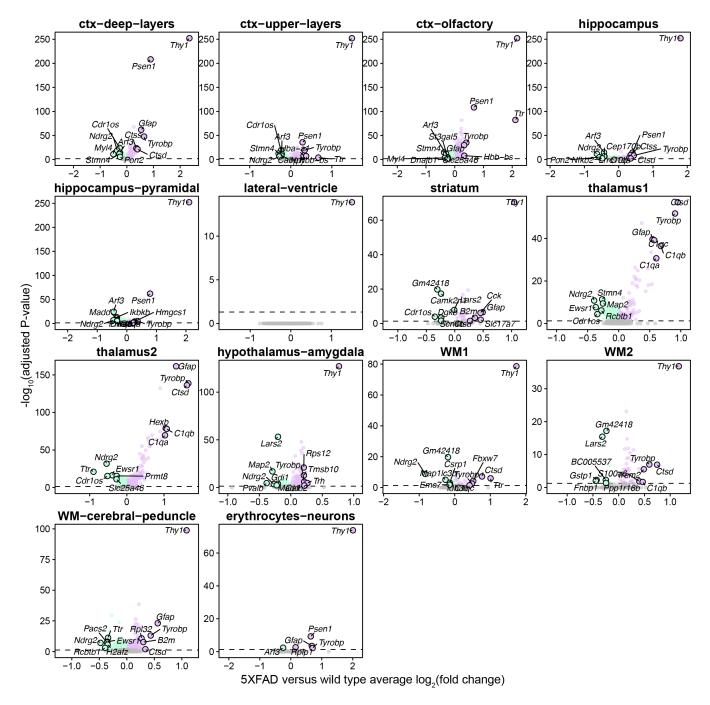


Fig. S16. 5xFAD versus wild type DEGs at four months of age. Volcano plots show the adjusted significance levels and effect sizes from the differential gene expression comparisons between 5xFAD versus wild type mice at four months of age. The results are shown for the differential gene expression analysis in each of the spatial transcriptomic clusters. The top and bottom six genes by effect size are annotated.

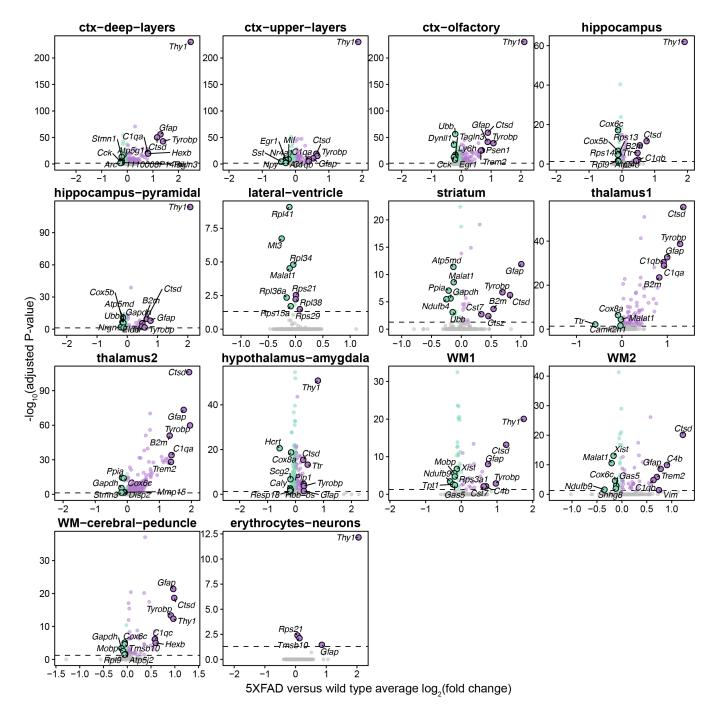


Fig. S17. 5xFAD versus wild type DEGs at six months of age. Volcano plots show the adjusted significance levels and effect sizes from the differential gene expression comparisons between 5xFAD versus wild type mice at six months of age. The results are shown for the differential gene expression analysis in each of the spatial transcriptomic clusters. The top and bottom six genes by effect size are annotated.

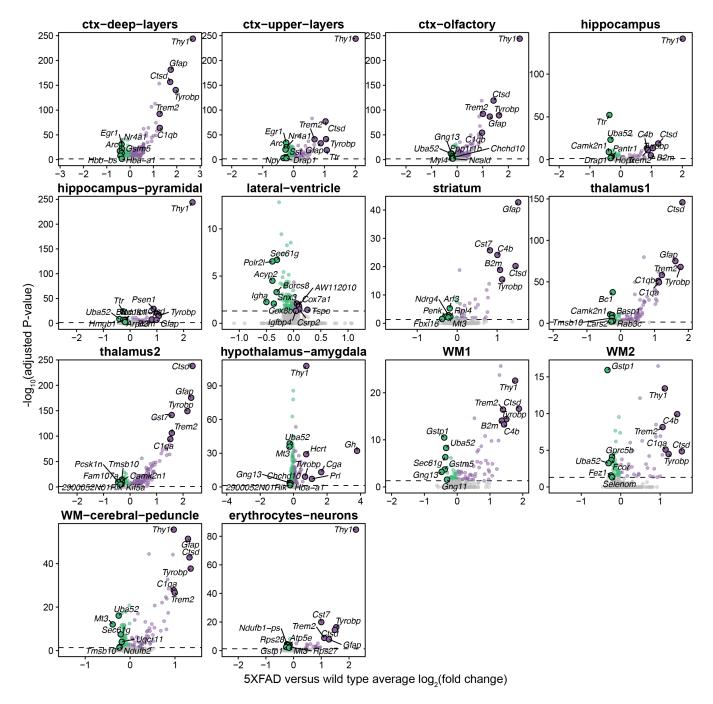


Fig. S18. 5xFAD versus wild type DEGs at eight months of age. Volcano plots show the adjusted significance levels and effect sizes from the differential gene expression comparisons between 5xFAD versus wild type mice at six months of age. The results are shown for the differential gene expression analysis in each of the spatial transcriptomic clusters. The top and bottom six genes by effect size are annotated.

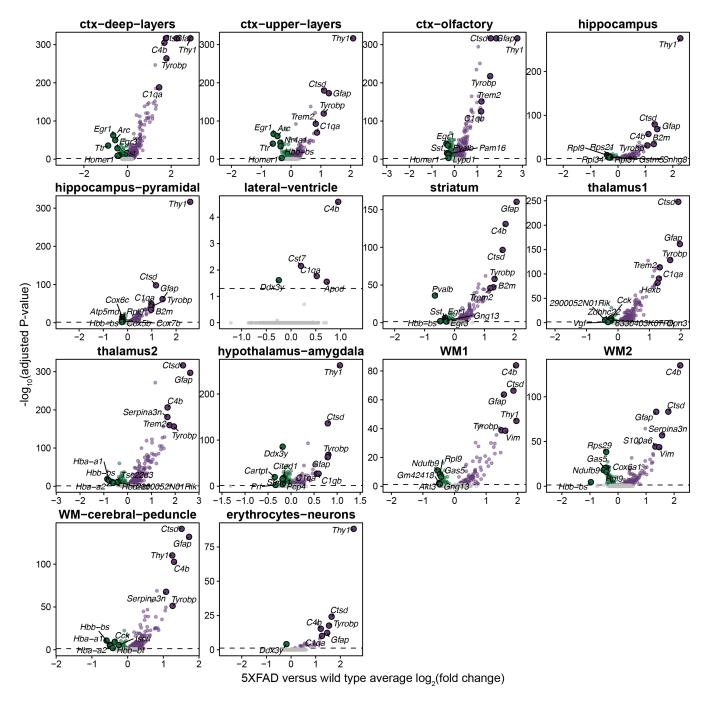


Fig. S19. 5xFAD versus wild type DEGs at twelve months of age. Volcano plots show the adjusted significance levels and effect sizes from the differential gene expression comparisons between 5xFAD versus wild type mice at six months of age. The results are shown for the differential gene expression analysis in each of the spatial transcriptomic clusters. The top and bottom six genes by effect size are annotated.

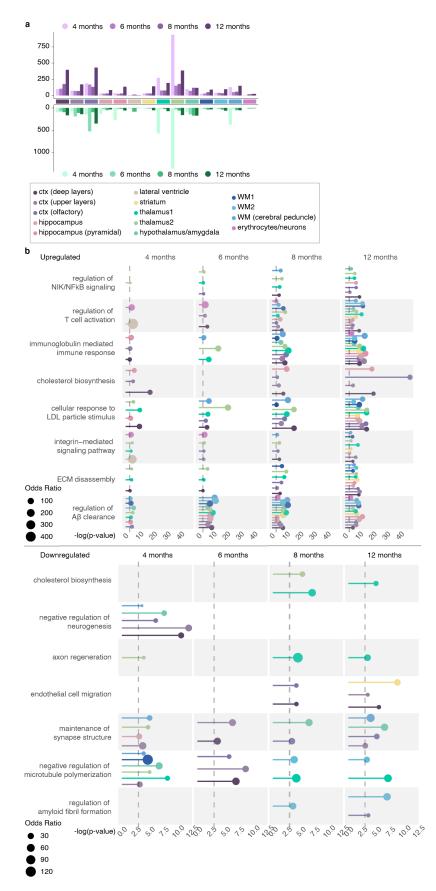


Fig. S20. Number of 5xFAD DEGs and GO term enrichment analysis. a, Barplot showing the number of DEGs in each group. b, Selected pathway enrichment analysis for the 5xFAD DEGs.

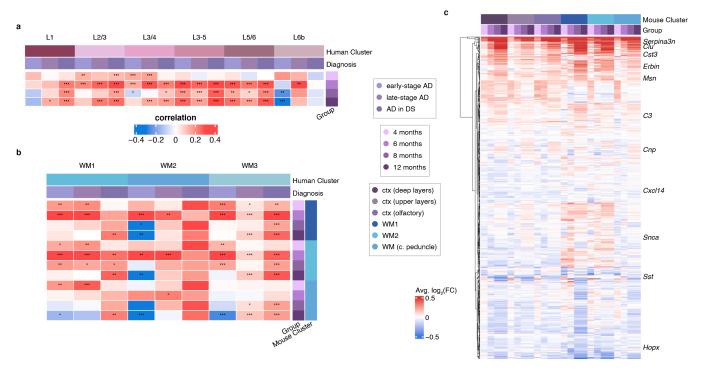


Fig. S21. Comparisons of human and mouse DEGs. a-b, Heatmaps showing correlations of effect sizes between human and mouse ST datasets in orthologous genes between human and mouse for cortical layer clusters a and white matter b clusters. c, Heatmap showing differential gene expression effect size results in the 5xFAD versus WT comparisons.

Fig. S22. Module hub gene networks for the human ST co-expression meta-modules. Hub gene networks for each of the 15 human spatial co-expression meta-modules. The top 25 hub genes ranked by kME are visualized. Nodes represent genes, and edges represent co-expression links.

M13 SCN1B MBOAT7 SYT7 PDXK MAPK8IP2 CADM3 FAIM2 DGKZ RBFOX3 USP22 GRIN1 PIP4K2B ATP9A PSD ATCAY CDIP1 SCN2B SPTBN4 FBXO44 AGAP3 KCNQ2 SLC8A2

PSMD6 PI4K2A MPG

M9 TSTD1 STK32C CKAP5 FXR2 NCEH1 NLGN2 TUBG2 CAB39 NUDT21 COPZ1 CSNK1D TMEM132AIP6K2 TUB HMOX2 FADS3 LRRTM3 DBN1 CHCHD6 MED15 PRXL2B

RPL38 RPS29 RPS23 RPS25 RPL37TPT1 RPS12 RPS6 FTH1 RPS27 RPL34 RPL37A RPL32 RPLP1 RPS27A RPL26 RPS18 RPL21 RPS8 RPS13 TMSB4X RPS24 RPS21 RPL41

М5

SOX2-OT ODPR ERMN PPP1R14A TF CRYAB SPP1 PIP4K2A DBNDD2 CNP CLDND1 PLP1 MOBP RNASE1 SELENOP MAG LAMP2 CLDN11 MBP SCD EVI2A MAL

M1

TNFRSF25 DLG4SLC25A23 M14 STMN1 ATP5MPL MIF COX7A2 MGST3 TMSB10 COX5B ATP5MD COX6C PPIA CALM2 HINT1 NDUFA4 COX7C HSPA8 DYNLL1 UQCRH SOD1 COX6A1 GAPDH COX7B ATP5MF NDUFB1 NDUFS5 ATP5IF1

M10 PIP5K1C_{GRK2} CACNA1A PLPPR2 KIF1A NAT8L DYNLL2 DLGAP4 NRXN2 CHD5 MIAT PTMS PDZD4 GALNT16 SYNPO ELK1 ARHGEF17 TNPO2 PALM

APP ACTB

M6 PEG3 PGM2L1 ELAVL4 NEGR1 ATP2B1 MAP2 PLCB1 GRIA2 ANK2 LMO4 SCN2A MEG3 CPE SPARCL1 PRKCB NECAB1 FBXW7 MAP1B SNHG14 GNA01 CNKSR2 CLIP3

SCN1A SNN ARNT2 SLC25A6 SEPTIN3 ENO1 TTC9B APBB1 CCT8 AAK1 SNCG SOD2 ACSL6 NEFH VSTM2A **KIF3A** CIT ATP5F1D KCNC1 RRAGA PARM1 CD59 RABAC1

M2

M15 TNS3 GJA1 ATP1A2 CGNL1 MT-CO2 MT-ATP6 MTRNR2L10 MT-ND1 MT-CO3 MT-ND1 ZIC2 MT-CYB MT-CO1 MT-ND4L MRVI1 MT-ND4 MT-ND5 MT-ND3 MT-ND2 MAP4K4 FBXL7 ERBIN TRIM56 KIF1C PAIP2B

CHGA ATP1A3 NEFM M11 AEBP1 ANGPTL4 СЗ IFITM2 SRGN IFITM3 AQP4 CNN3 PTTG1IP IGFBP7 VIM CLU SERPINA3 TUBB2B CD44 HLA-E STOM CEBPD AHCYL1 CLDN5 TIMP1 PLEC C1QB DEPP1 CD99

DKK3 CALY BSCL2 SNCB PKM NEFL SLC17A7 CLSTN1 ENC1 DNM1 TMEM130 ENO2 THY1 TMEM59L PLD3 NCDN PHYHIP STMN3 RAB6B PRKAR18 CABP1 SYP

M7

SYN1 CALM3 IDS GNAS SYT1 CHN1 VSNL1 NRGN GABRA1 SNAP25 PPP3CA BASP1 NPTX1 OLFM1 GPM6A RBFOX1 TSPYL1 STMN2 CALM1 SYT4 ATP2B2 CAMK2A YWHAB

МЗ

TRO L3MBTL2 KLF16 GFOD2 ZFYVE27 PNPO CAPRIN2 SORCS1 MFSD10 GRAMD4 CIAO3 SRA1 M12 ADD3 NCL TTLL7 ANP32B SEPTIN7 DST CCDC88A ANKRD12 KIF5B MALAT1 HSP90AA1KTN1 DYNC112 MAN1A2 SEC62 GOLGA4 HMGB1 NAP1L1 SMARCA5 ZC3H13 BPTF ATRX PABPC1

M8 RHPN1 NEU1 CENPT ASIC2 ATP2B3 PDE4A RELL2 CELF3 HDAC3 PGP FNDC10

BEX1 ATP1A1 PREPL NDRG4 SYN2 TUBB2A YWHAH TAGLN3 ССК RTN1 TUBA1B YWHAG UCHL1 RGS4 SERPINI1 TSPAN7 MDH1 YWHAZ NSF STXBP1 GAP43 PNMA2 NPTN EIF4A2SNRPN

Μ4

а	Control F, 74	Control M, 70	earlyAD F, 89	earlyAD M, 90	AD F, 89	AD F, 90	AD_DS F, 56	$^{AD_DS}_{F,62}$ b ₂₇
M1		18	and a			All	17	
M2	Ø						N	
M3			1	()			N	
M4	Ø		1 a	UP.			N	
M5	3		4	C		The	N	
M6	Ø		77	()			R	
M7	Ø		22	U			17	
M8	Ø	\bigcirc		()			N	
6W		\bigcirc		()			Z	
M10	Ø			()			D	
M11		\bigcirc	12	()			J.	
M12	P		23				N	
M13	T	Contract of the second	de la	O			15	
M14	Ċ	O	12				N.	
M15		O	110					
								i je je je wi
								Control earlyAD AD AD_DS

Fig. S23. Module eigengenes for the human ST meta-modules. a, Spatial feature plots showing module eigengenes (MEs) for the 15 human co-expression meta-modules shown in eight representative samples. b, ME distributions in each disease group (control, early-stage AD, late-stage AD, AD in DS) stratified by cortical layer clusters and white matter.

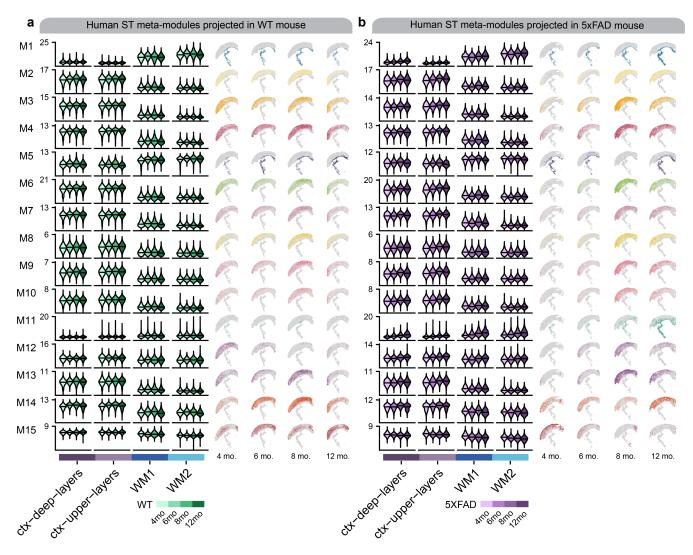


Fig. S24. Module eigengenes of human co-expression meta-modules in the mouse ST dataset. a-b, Left: Module eigengene (ME) distributions for the 15 human co-expression meta-modules in each mouse age group (control, early-stage AD, late-stage AD, AD in DS) stratified by cortical and white matter clusters. Right: Spatial feature plots showing MEs in four representative samples. Panel a shows the results in wild type mice and panel **b** shows the results in 5xFAD.

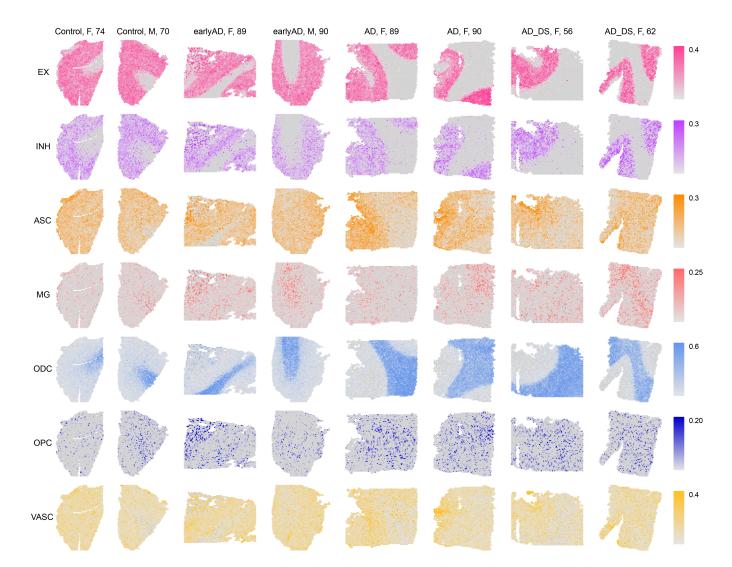


Fig. S25. Cell-type deconvolution results in the human ST dataset. Spatial feature plots in eight representative samples from the human ST dataset showing the inferred proportion of different major cell types based on our deconvolution analysis conducted with SPOTLight⁴.

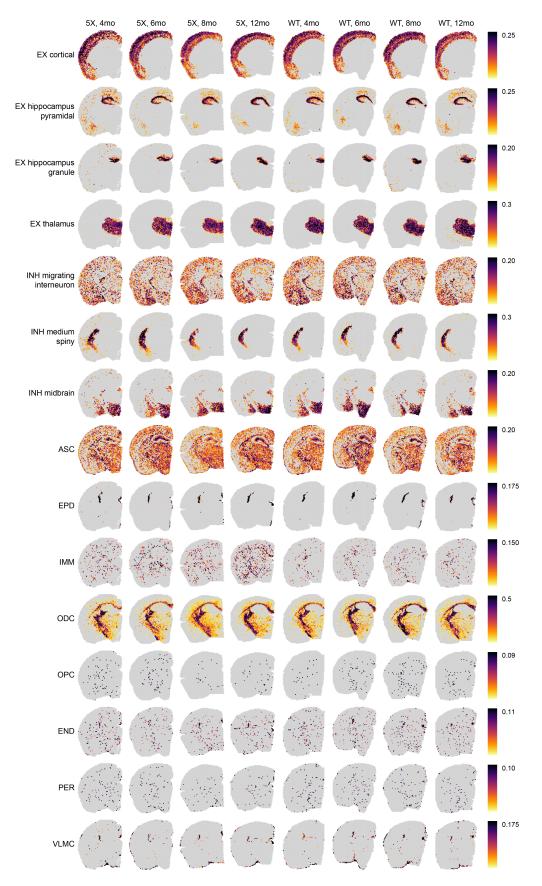


Fig. S26. Cell-type deconvolution results in the mouse ST dataset. Spatial feature plots in eight representative samples from the mouse ST dataset showing the inferred proportion of different major cell types based on our deconvolution analysis conducted with SPOTLight⁴.

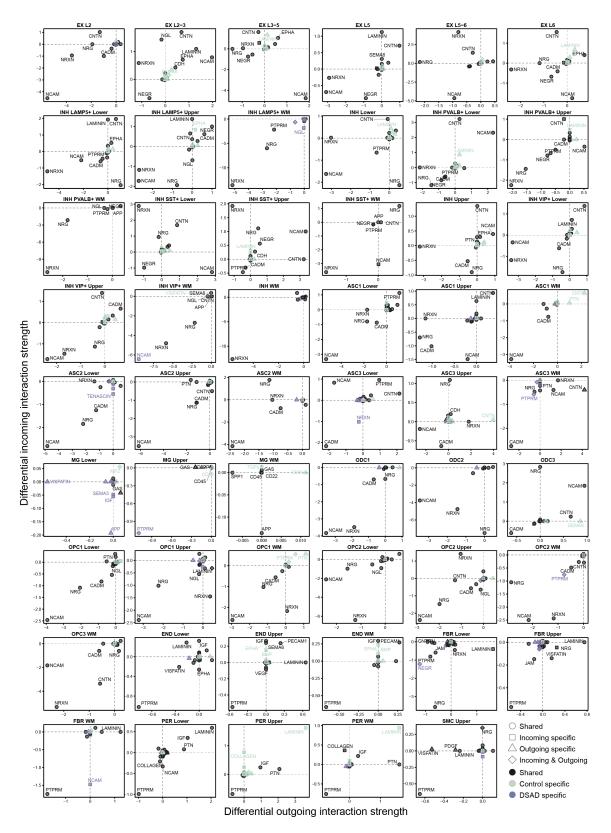


Fig. S27. Differential cell-cell signaling between AD in DS and control. Scatter plots showing the differential outgoing interaction strength versus the differential incoming interaction strength from the differential cell-cell signaling network analysis between AD in DS cases versus cognitively normal controls. Pathways were shown in each cluster where there was a statistically significant (p-value < 0.05) difference between AD in DS and control based on a permutation test ⁵.

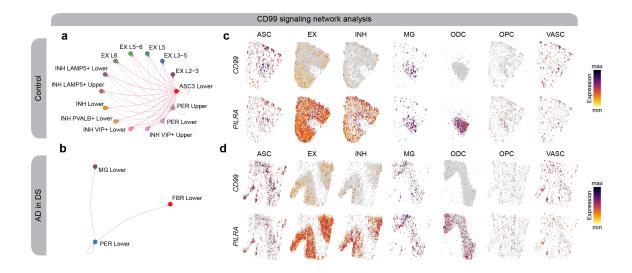


Fig. S28. CD99 signaling changes between AD in DS and control. textbfa-b, Network plot showing the CCC signaling strength between different cell populations in controls (a) and AD in DS (b) for the CD99 signaling pathway. c-d, Spatial feature plots of the snRNA-seq in predicted spatial coordinates for one control sample (c) and one AD in DS sample (d) for one ligand and one receptor in the CD99 pathway.



Fig. S29. Integration of amyloid plaque imaging (Amylo-glo) and hotspot analysis in the human ST dataset Spatial feature plots for the human ST dataset showing the integration of amyloid plaque imaging of Amylo-glo. a, The Amylo-glo score, computed as the sum of the areas (size) for all overlapping amyloid plaques with each ST spot, and then log normalized. b, Getis-Ord Gi* hotspot analysis based on the Amylo-glo score.

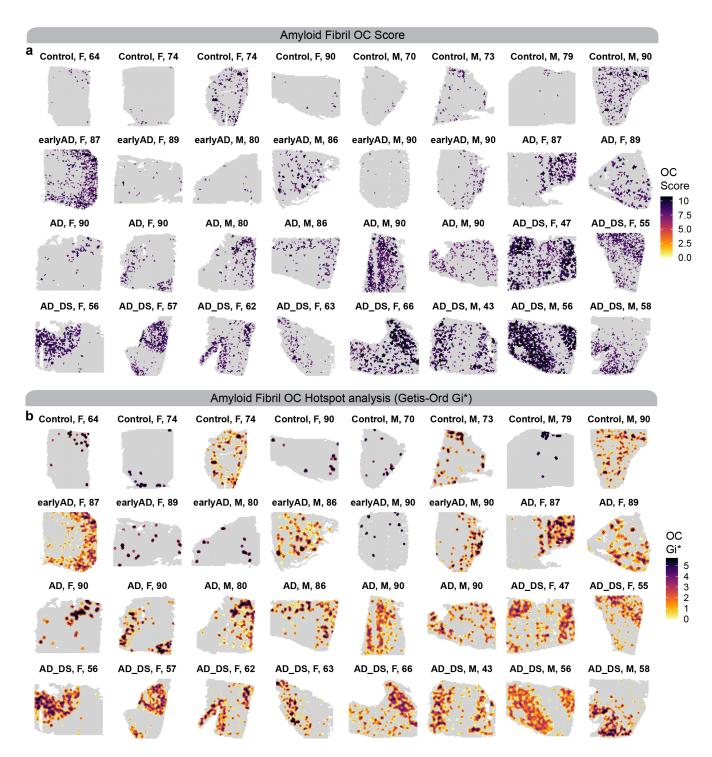


Fig. S30. Integration of amyloid fibril imaging (OC) and hotspot analysis in the human ST dataset. Spatial feature plots for the human ST dataset showing the integration of amyloid fibril imaging of OC. a, The OC score, computed as the sum of the areas (size) for all overlapping amyloid plaques with each ST spot, and then log normalized. b, Getis-Ord Gi* hotspot analysis based on the OC score.

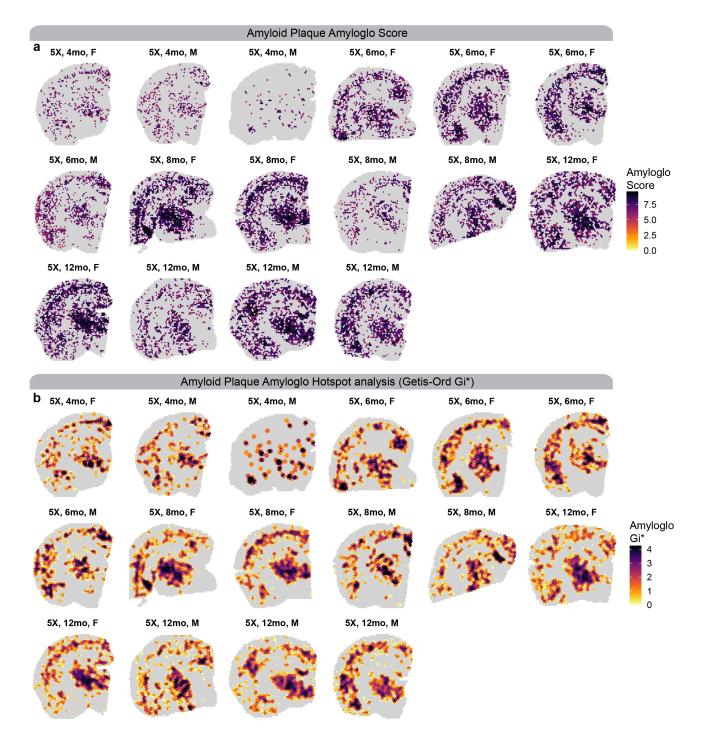


Fig. S31. Integration of amyloid plaque imaging (Amylo-glo) and hotspot analysis in the mouse ST dataset Spatial feature plots for the mouse ST dataset showing the integration of amyloid plaque imaging of Amylo-glo. a, The Amylo-glo score, computed as the sum of the areas (size) for all overlapping amyloid plaques with each ST spot, and then log normalized. b, Getis-Ord Gi* hotspot analysis based on the Amylo-glo score.

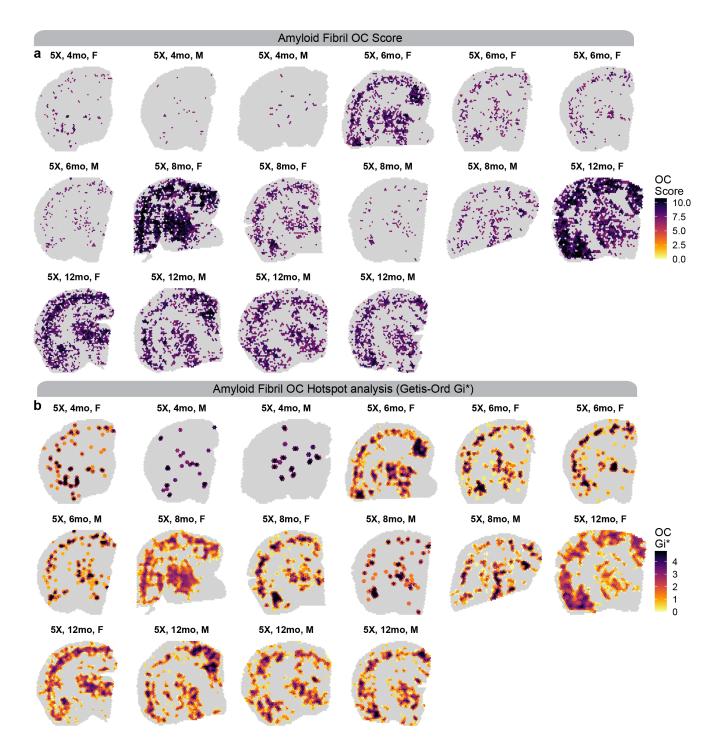


Fig. S32. Integration of amyloid fibril imaging (OC) and hotspot analysis in the mouse ST dataset Spatial feature plots for the mouse ST dataset showing the integration of amyloid fibril imaging of OC. a, The OC score, computed as the sum of the areas (size) for all overlapping amyloid plaques with each ST spot, and then log normalized. b, Getis-Ord Gi* hotspot analysis based on the OC score.

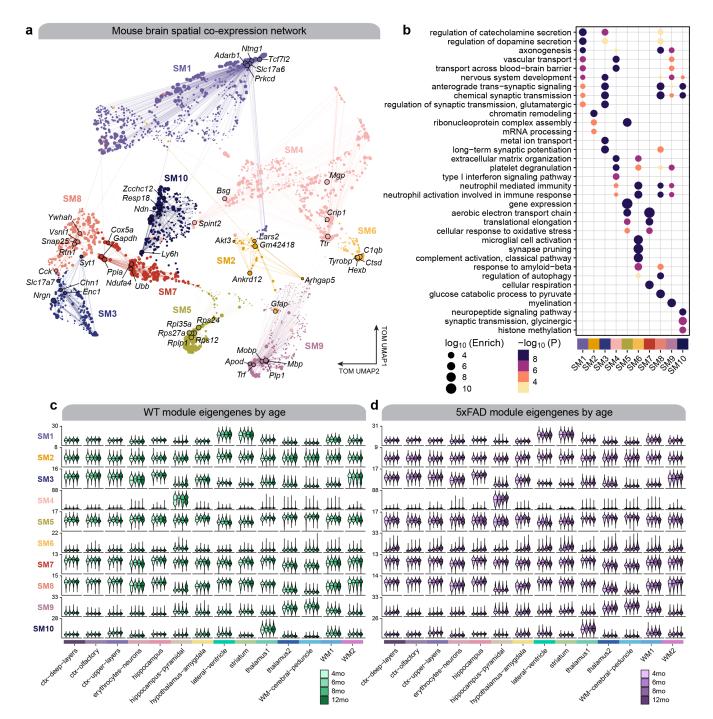


Fig. S33. Co-expression network analysis in the mouse ST dataset a, UMAP plot of the mouse spatial co-expression network. Each node represents a single gene, and edges represent co-expression links between genes and module hub genes. Point size is scaled by eigengene-based connectivity. Nodes are colored by co-expression module assignment. The top five hub genes per module are labeled. Network edges were downsampled for visual clarity. **b**, Dot plot showing selected GO enrichment results for each co-expression module. **c-d**, Module eigengene (ME) distributions for the ten mouse co-expression modules in each mouse age group (control, early-stage AD, late-stage AD, AD in DS) stratified by cluster for wild type (**c**) and 5xFAD mice (**d**).

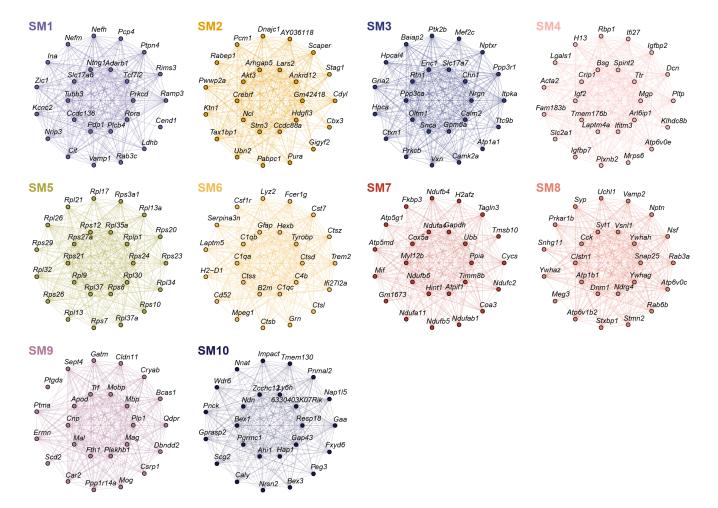


Fig. S34. Module hub gene networks from the mouse co-expression network analysis Hub gene networks for each of the 10 mouse spatial co-expression modules. The top 25 hub genes ranked by kME are visualized. Nodes represent genes, and edges represent co-expression links.

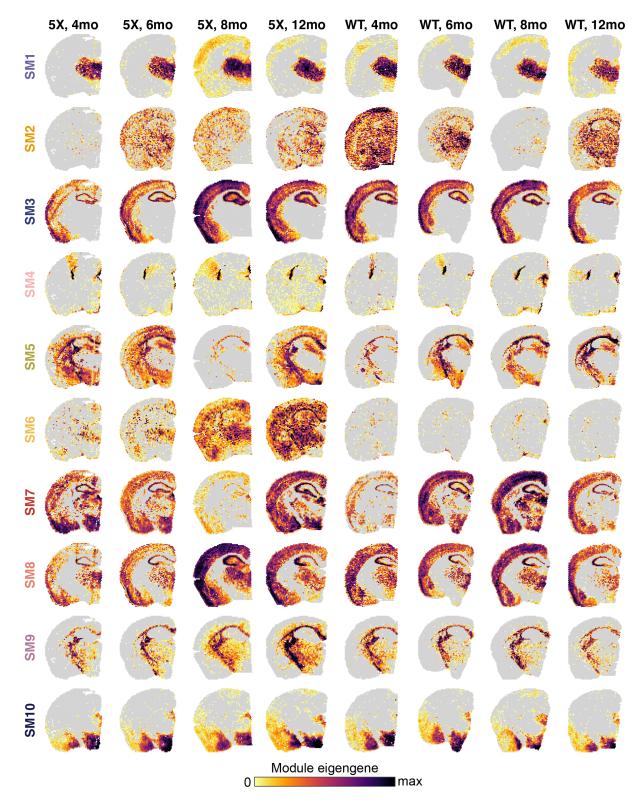


Fig. S35. Module eigengenes in representative samples from the mouse ST dataset Spatial feature plots showing module eigengenes (MEs) for the ten mouse co-expression modules shown in eight representative samples.

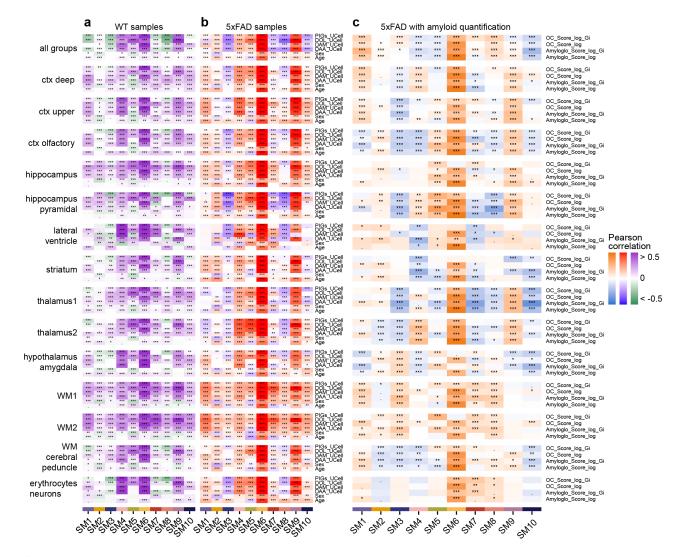


Fig. S36. Module-trait correlation analysis in the mouse co-expression network a-b, Heatmap showing the module-trait correlation results for age, sex (positive correlation corresponds to female), and gene signatures for plaque-induced genes (PIGs), disease-associated oligodendrocytes (DOL), disease-associated microglia (DAM), and disease-associated astrocytes (DAA) in wild type (a) and in 5xFAD (b) mice. c, Heatmap showing the module-trait correlation results with the amyloid imaging analysis (Amylo-glo and OC) in 5xFAD with amyloid quantifications. Not significant (ns), p > 0.05; * p <= 0.05; ** p <= 0.01; *** p <= 0.001.

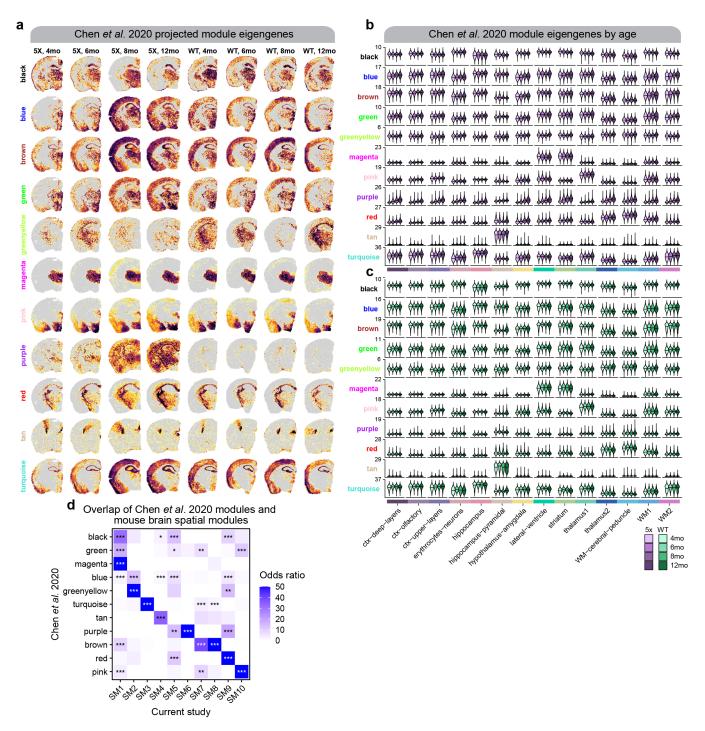


Fig. S37. Investigating the gene co-expression modules from Chen et al in our 5xFAD ST dataset a, Spatial feature plots showing module eigengenes (MEs) for the ten mouse co-expression modules shown in eight representative samples. **b-c**, Module eigengene (ME) distributions for the ten mouse co-expression modules in each mouse age group (control, early-stage AD, late-stage AD, AD in DS) stratified by cluster for 5xFAD (b) and 5xFAD mice (c). **d**, Heatmap showing gene set overlap analysis results comparing the sets of genes from the mouse ST co-expression modules with the co-expression modules identified from the Chen et al. ⁶ study. Fisher's exact test results shown as follows: Not significant (ns), p > 0.05; * p <= 0.05; ** p <= 0.01; *** p <= 0.001.

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